TRPM2 channel: New Drug Targets for Treating Brain Ischemia

Abstract: Activation of the transient receptor potential melastatin 2 (TRPM2) channel is involved in the responses to oxidative stress under pathological processes such as ischemia injury. Accumulating evidence indicates that TRPM2 channel can be activated by several factors, such as ADP-ribose (ADPR), H2O2, calcium and temperature, which imply the mechanisms of TRPM2 activation are very complex. Our recent studies have identified the ligand binding pocket of TRPM2 by ADPR or cADPR, and uncovered the TRPM2 inactivation mechanisms by proton, zinc and copper. Based on these studies, we developed several compounds that inhibit TRPM2 activity either interact with pore region or competing with agonists. Furthermore, our results clearly showed one of these compounds significantly reduced the brain ischemia injury in mice tMCAO model, suggesting that the compound targeting to TRPM2 have a potential therapeutic value for treating brain ischemia. Our study sheds the new light on the drug development for stroke.